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New targets of therapy in T-cell lymphomas

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Introduction and background on TCL

T-cell lymphomas (TCL) are a group of lymphoid malignancies of mature (i.e. post-thymic) T-cell derivation characterized by striking clinico-pathological diversity, aggressive course and poor response to therapy [1]. TCL have an inferior outcome compared to B-cell lymphomas, even when stratified according to validated lymphoma risk-assessment tools, such as the international prognostic index (IPI) [2-4]. Recently, more specific prognostic indexes have been developed for selected subtypes of TCL [5]. However, stringent predictive biomarkers for response to therapy and survival in TCL remain to be discovered.

TCL account for 13-15% of the approximately 60,000 non Hodgkin's lymphomas (NHL) diagnosed annually in the U.S. This results in an estimate of 8,000-9,000 new cases of TCL per year [6-7]. Thus, although individually each type of TCL is relatively rare, the cumulative burden presented by these malignancies is very significant. The epidemiology of various types of TCL, particularly the association with environmental risk factors such as lymphotropic viruses, differs substantially across the globe. In parts of Asia, South-Central America, and the Middle East, TCL may represent as much as 35-40% of all the NHL and are frequently associated with the Epstein Barr Virus (EBV) and the Human T-lymphotropic Virus 1 (HTLV-1) [8]. Association with EBV has been observed also in a significant fraction of TCL in the U.S. and Europe, but the role that EBV and other human lymphotropic viruses, other than HTLV-1, play in the development and the outcome of TCL is presently unknown [9].

The clinical and pathological characterization of TCL has continued to be refined over the recent past. The Working Formulation (WF) failed to recognize these disorders as distinct disease entities, with the exception of Mycosis Fungoides (MF), T-cell Lymphoblastic Lymphoma (TLBL), and HTLV-1 related adult-cell leukemia-lymphoma (ATLL). This hindered the descriptive epidemiology of TCL and delayed the analysis of specific incidence rates, natural history and outcome. Even with the introduction of more accurate diagnostic tools, such as lineage-specific and differentiation-specific monoclonal antibodies (mAb), and DNA-based antigen receptor clonality assays, the identification of many types of TCL has been mired by the lack of convenient flow cytometric clonality markers for T-cells, by a remarkable pathological diversity, and by substantial clinical overlap with non-malignant, T-

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cell mediated, inflammatory disorders. Adding to this complexity, pathologic prognostic criteria long validated in B-cell lymphomas, such histologic grade, cytologic features, and patterns of lymph node involvement (diffuse versus nodular) could not be consistently applied to TCL [10-11].

The great majority of TCL derive from the malignant transformation of post-thymic T-cells, hence their histogenetic definition as peripheral T-cell lymphomas (PTCL), as opposed to lymphomas of precursor T-cell origin, such as T-LBL [12]. However, while a germinal center (GC) histogenetic model for B-cell lymphomas has been developed and validated over the past 10 years [13], the identity and anatomical distribution of the normal human T-cell subsets that give origin to the various types of TCL remain for the most part unknown, with the important exception of angioimmunoblastic T-cell lymphoma (AITL), which is very likely to originate from the recently identified follicular helper T-cell (TFH) [14-16]. The lack of a hypothesis-generating model for human T-cell lymphomagenesis, together with the scarcity of good animal models, continues to hamper progress in the treatment of TCL.

The clinical aspects of each specific disease entity have increasingly assumed a crucial role in diagnosis and risk stratification of TCL. Subsets of TCL with predominant nodal, extranodal, or leukemic involvement are now recognized (Table 1), often with significant prognostic implications. For clinical purposes, TCL can be conveniently divided in two groups: one that primarily involves the skin and one that involves lymph nodes or other extranodal sites. Most skin-limited TCL, generically defined as cutaneous T-cell lymphomas (CTCL), are chronic, relapsing malignancies, characterized by rash, pruritus, fatigue, and susceptibility to infections due to a break down of the barrier protection and the innate immunity provided by the skin.

The most common types of CTCL are Mycosis Fungoides (MF), a disease of CD4+, chemokine receptor 4 (CCR4)-positive, cutaneous lymphocyte-associated antigen (CLA)-positive, variably CD25+ skin-homing memory T-cells and its leukemic variant, Sezary Syndrome (SS) [17-18]. Non-MF/SS types of CTCL are less frequent and, with the exception of primary cutaneous CD30+ anaplastic large cell lymphoma (pcALCL), tend to have a slightly more aggressive clinical course [10]. While CTCL patients often receive prolonged skin-directed therapy, such as topical steroids, ultraviolet light, and electron beam radiation, many eventually go on to require systemic therapy [19]. Once systemic therapy is required, the major clinical challenge is represented by the short duration of response, hence the emphasis on the use of maintenance therapy. With a prolonged survival and generally good performance status, patients with symptomatic CTCL often receive sequentially a variety of systemic therapies, none of which however is curative. Thus, there is a continuous need for novel agents with better and more durable clinical activity in CTCL. In addition, better prognostic factors need to be developed so that patients with more aggressive or treatment-resistant forms of CTCL can be identified early and can be offered more intensive or investigational therapies, including allogeneic hematopoietic stem cell transplantation (HSCT).

The group of TCL affecting primarily the lymph nodes and non-cutaneous extranodal sites includes most of the diseases originally identified as PTCL. These are aggressive, systemic malignancies characterized by advanced stage at presentation, extensive extranodal involvement, often rapid clinical progression and low complete response (CR) rate, even with intensive combination chemotherapy [1]. Patients with PTCL are more likely to be older adults presenting with poor performance status, prominent B symptoms, and cytokine-mediated syndromes such as anasarca, hemophagocytosis, vascular leak syndrome, hypoalbuminemia, thrombocytopenia, and eosinophilia. In addition to lymph nodes, bone

marrow, liver, and spleen, PTCL may also involve the skin as a secondary extranodal site. It is important to recognize that skin involvement in PTCL does not portend the same favorable prognosis that is observed in CTCL. PTCL have one of the lowest 5-year disease-free survival (DFS) of all the subtypes of NHL [20]. While front-line doxorubicin-based combination chemo-immunotherapy cures greater than 50% of DLBCL [21], the 5-year overall survival in PTCL is only 25%-30% [22]. Considering the higher incidence of poor risk features in PTCL such as older age, advanced stage, and multiple extranodal sites, it was a matter of debate whether T-cell lineage *per se* was prognostically relevant. However, it is now recognized that one of the reasons for the suboptimal response rate observed in TCL is a high rate of resistance to drug-induced apoptosis [23]. Novel front line chemotherapy regimens and chemo-immunotherapy combinations are being explored in PTCL, but with the treatments currently employed the majority of patients experience disease recurrence or progression within 1-2 years. Patients with relapsed disease have limited therapeutic options and respond poorly to further conventional treatments, including high-dose chemotherapy and autologous stem cell transplantation (HDCT/SCT).

A fundamental challenge in the study of TCL remains the translation of the rapidly increasing body of knowledge on T-cell biology and molecular genetics into risk stratification and targeted therapies. With few exceptions, such as hepatosplenic and subcutaneous panniculitis-like lymphomas, where expression of the αβ T-cell receptor (TCR) as opposed to the γδ TCR identifies a subset with a more favorable prognosis, the clinical relevance of the expression of markers, such as CD8, CD4, CD56, cytotoxic markers (TIA-1, Granzyme B), EBV, and a variety of oncogenes, cytokine and chemokine receptors, remain to be determined [2-3, 24-30]. Several excellent reviews on the diagnostic and clinical aspects of the major types of TCL have been published recently [1, 22, 31-32]. The goal of this review is to provide a synthetic summary of the drugs that have been recently approved or are in advanced phase of development for the management of CTCL and PTCL. For a detailed discussion on the respective role of each agent in the management of specific TCL subtypes, the reader is referred to the referenced work.

1. MONOCLONAL ANTIBODIES

a. Zanolimumab (HuMax – anti-CD4 mAb)

Zanolimumab is a fully human IgG1 kappa monoclonal antibody (mAb) directed against the CD4 antigen [33], the MHC class II co-receptor that is characteristic of T helper cells [34]. This marker is specific for T cells, being expressed only weakly on monocytes, macrophages and Langerhans cells, and is thus an ideal antigen for molecular targeting. While zanolimumab was originally tested in the settings of rheumatoid arthritis and psoriasis [35-36], it gained momentum more recently in therapeutic trials against T-cell malignancies. Early pilot studies had shown that murine anti-CD4 mAbs produced objective responses in a small number of CTCL patients [37]. More recently, two phase 2 studies were conducted in parallel looking at the effect of zanolimumab in both early-stage CTCL and late-stage, treatment-refractory CTCL [38]. Twenty-seven patients with early-stage MF were treated with either 280 mg or 560 mg weekly zanolimumab infusions (first of the two studies), while 13 patients with late-stage, treatment-refractory MF and 9 patients with SS were treated with either 280 mg or 980 mg weekly infusions of the study drug. Objective responses (as assessed in terms of index lesion scores) were recorded in 13 MF patients and 2 SS patients. In the higher-dosed groups (560 and 980 mg doses), a response rate of 56% was observed. Infections and eczematous dermatitis were the most frequent adverse events. Based on these encouraging data, Phase III trials were initiated in CTCL and PTCL.

The mechanism of zanolimumab has proven to be multifaceted. Recent work from Rider *et al*. showed three distinct pathways by which zanolimumab acts [39]. Firstly, the CD4

tyrosine kinase $p56_{lck}$ is uncoupled from the TCR and transmits inhibitory signals via Dok-1 and SHIP-1 inhibitor molecules. Secondly, it acts conventionally as opsonization to enhance cell-mediated killing of the CD4+ cells. Lastly, it down-regulates CD4 from the cell surface via a slow Fc-dependent mechanism. Which of these mechanisms is most relevant in producing the antibody's anti-tumor effect *in vivo* is currently unknown. Despite its promising activity, Zanolimumab's clinical development in both CTCL and PTCL was unfortunately interrupted due to the pharmaceutical company's (Genmab A/S, Denmark) decision to revise its strategic portfolio and marketing plans [40]. The fate of Zanolimumab as a novel therapeutic agent in TCL is therefore unknown at this point.

b. Anti-CD30 mAbs (SGN-30, MDX-060, MDX-1401, SGN-35)

CD30 is a transmembrane glycoprotein and a member of the TNF family [41] that is expressed on activated B-cells and T-cells. Initially identified as the Ki-1 antigen on Reed-Sternberg cells in Hodgkin lymphoma (HL) [42], it has since been shown to have a relatively restricted distribution in a subset of mature T-cell leukemias and PTCL [43]. While the intrinsic role of CD30 has not been well-defined, it has been observed that, under some conditions, ligation of CD30 induces cell death [44,45]. As such, various monoclonal antibodies directed against it are currently under investigation.

MDX-060, a fully human anti-CD30 IgG1 kappa monoclonal antibody, recently underwent a phase I/II trial in HL and anaplastic large-cell lymphoma (ALCL) [46]. 21 patients (16 with HL) were treated in the phase I portion with no maximum tolerated dose (MTD) being defined. An additional 51 patients (47 with HL) were treated in the phase II portion. Six patients had clinical response, and 25 patients had stable disease while on trial. Five patients remained progression free at 1 year. Based on these data, MDX-060 is being studied currently in combination with other therapies.

SGN-30, a chimeric anti-CD30 antibody composed of human γ1 and κ constant regions genetically fused to the V_{HS} and V_{LS} regions from AC10, a murine anti-human CD30 monoclonal antibody, has demonstrated antitumor activity in cell-line models of HL [45]. In terms of its mechanism, depletion of macrophages has recently been shown to markedly reduce the efficacy of SGN-30 [47]. Clinical data on the use of SGN-30 in humans are not available currently.

Medarex Inc. and BioWa Inc. announced in January 2007 the introduction of a fully human anti-CD30 antibody, MDX-1401, for which a Phase I clinical trial enrolling up to 36 patients is underway [48]. Clinical data are not currently available.

SGN-35 (Brentuximab vedotin, Seattle Genetics, Inc.) is a new antibody-drug conjugate comprising an anti-CD30 antibody attached to the potent synthetic drug monomethyl auristatin E (MMAE) by an enzyme cleavable linker. SGN-35 is stable in the bloodstream, but releases MMAE upon internalization into CD30-expressing tumor cells, resulting in targeted cell-killing. SGN-35 has shown very encouraging preliminary activity in HL and ALCL. In a phase I dose-escalation study, 45 patients received SGN-35 every three weeks, at doses ranging from 0.1 milligrams per kilogram (mg/kg) to 3.6 mg/kg [49]. Among 28 evaluable Hodgkin lymphoma and systemic ALCL patients treated at doses of 1.2 mg/kg and higher, the overall response rate was 54-57%. At the higher dose levels, the complete response rate was 32-39%. The median duration of response was 7.3 months. A single-agent phase II study of SGN-35 in relapsed and refractory systemic ALCL, as well as a phase II study evaluating the potential for retreatment with SGN-35 in patients who have relapsed after discontinuing previous SGN-35 therapy are in progress.

c. Siplizumab (MEDI-507 – anti-CD2 mAb)

CD2 is a cell marker expressed on all mature T-cells and most natural killer (NK) cells [50]. It appears early in thymocyte development. This marker is upregulated on activated T-cells as compared to those in a resting state. Siplizumab (MEDI-507), an anti-CD2 humanized monoclonal antibody genetically engineered from the rat version of the same antibody (BTI-322), was initially studied in murine models of ATL. Mice engrafted with a human HTLV-1-positive T-cell leukemia survived longer when treated with siplizumab compared to those treated with an anti-CD25 monoclonal antibody and prolonged treatment resulted in better outcomes than shorter treatment [51]. Based on such preliminary data, phase I trials in humans were conducted in CD2-positive lymphomas/leukemias [ASCO meeting 2005 abstract 2533; ASH meeting 2006 abstract 2727]. In the 2006 report, 15/16 treated patients had CTCL (6) or PTCL (9). One patient with PTCL achieved a CR. Dose-limiting toxicites included dermatitis and pulmonary edema. No maximum tolerated dose was established. More recent data suggest an increased incidence of EBV-induced B-cell lymphoproliferative disease (LPD) in patients treated with siplizumab. Of 29 patients treated with the drug, 4 (13.7%) developed EBV-mediated LPD, resulting in cessation of the trial [52].

d. Alemtuzumab (Campath-1H – anti-CD52)

Alemtuzumab is an unconjugated humanized IgG1 kappa mAb directed against the CD52 antigen, a glycoprotein highly expressed on all B and T lymphocytes, monocytes, macrophages, eosinophils, natural killer cells and dendritic cells [53]. CD52 is also variably expressed on subsets of tumor cells, especially T-prolymphocytic leukemia (T-PLL), B-cell chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), acute lymphoid leukemia (ALL) and NHL including TCL [54]. However, in contrast to B-cell malignancies, there is a great variability in the expression of CD52 in TCL. For instance, CD52 is expressed in only 35-40% of peripheral T cell lymphomas not otherwise specified (PTCL-NOS) at the same level as in normal T-cells [55]. In 2001 alemtuzumab was approved in the United States and Europe for the treatment of relapsed/refractory B-cell chronic lymphocytic leukemia (B-CLL) and, more recently, in September 2007, the FDA expanded the labeling to untreated B-CLL. The standard regimen consists of 2-hour intravenous (IV) infusion, at a starting dose of 3 mg on day 1, 10 mg on day 2 up to a target dose of 30 mg, three times weekly for a total of 8-12 weeks. While typical infusional toxicity has been appreciated, the major adverse events seen with alemtuzumab have included devastating opportunistic infections and sepsis with wide-ranging sites of infection and pathogens.

Several studies have shown alemtuzumab to be active in TCL [56-59]. However, the clinical experience with alemtuzumab in TCL has been limited to small series and approval for this indication has not yet been granted. In a European multicenter phase II trial, 50 NHL patients, among whom 8 had advanced refractory MF, were treated with alemtuzumab: a response rate of 50% with 2 CRs was seen [60]. This preliminary experience led to the largest reported CTCL series in which 22 patients with advanced MF/SS were treated with single agent alemtuzumab administered intravenously at the standard dose of 30 mg for up to 12 weeks: the overall response rate (ORR) was 55% (32% complete response, CR and 23% partial response, PR) with a better efficacy in patients with early stage of disease (erythroderma versus skin tumors). The reported disease-free survival (DFS) was 12 months [57]. In another study, 8 patients with MF/SS, 7 of which with refractory disease, were treated with alemtuzumab according to the standard schedule, a lower response rate was achieved (the ORR was 38% with no CR observed) and a shorter DFS (4 months) was obtained [61]. In the attempt to reduce the serious side effects (especially opportunistic infections) seen with the standard schedule, Zinzani *et al.* preliminarily reported that reduced-dose alemtuzumab (10 mg three times a week for 4 weeks) had clinical activity in 10 pretreated T-cell lymphomas (6 PTCL-NOS and 4 MF) with an ORR of 60 % and 20% of

CRs (the CR rate was higher (33%) in the PTCL group) [58]. A favorable experience combining the low dose and the subcutaneous (SQ) administration of single agent alemtuzumab has been recently reported by Bernengo *et al*.: 14 SS patients were treated with alemtuzumab, 10-15 mg thrice weekly, for a shorter period of time, individually based on the presence or absence of circulating Sezary cells [59]. The ORR was 85.7% with a 21.4% CR and a disease free survival (DFS) of 12 months after a median follow-up of 16 months. Alemtuzumab was also safely administered subcutaneously to 5 octogenarian CTCL patients, among whom 3 had refractory/relapsed MF [62]. All patients responded; three achieved durable responses (18 to 28+ months).

The data on PTCL treated with single agent alemtuzumab are scarce. The only prospective trial in PTLC patients treated with single agent alemtuzumab was published about five years ago [63]. Fourteen patients with advanced relapsed or chemo-refractory PTCL were treated with IV alemtuzumab with the standard schedule. The ORR was 36% with 3 patients achieving a CR and 2 a PR. 2 of the 3 patients in CR obtained a durable response (6 and 12 months). Alemtuzumab has showed to possess clinical activity in T-cell lymphomas but single agent approach does not appear to be curative. To possibly enhance the therapeutic efficacy, alemtuzumab-based combination regimens are emerging.

A number of small preliminary studies in which alemtuzumab has been administered in association with single agent chemotherapy (pentostatin) or with polychemotherapy (CHOP or DHAP) in newly diagnosed or pretreated T-cell lymphoma patients have been presented with response rates varying from 75% in the newly diagnosed patients to 50% in the relapsed/refractory subpopulation [64,65; ASH meeting 2006 abstract 4971; ASCO meeting 2006 abstract 7594]. And overall response rate of 85% was seen in a more recent study of CHOP given every 14 days along with alemtuzumab given as a 30-mg subcutaneous injection on days 1, 5 and 10 [ASH meeting 2008; abstract 1999]. The association of alemtuzumab with monoclonal antibodies such as anti-CD4, retinoids, histone deacetylase inhibitors and other emerging class of new agents should be investigated. Alemtuzumab therapy administered with proper antimicrobial therapy is feasible and effective in TCL, and this approach may translate into survival benefit. Viral reactivation and hematologic toxicity are a major concern. The infusion-related events are significantly reduced by the SQ administration without obvious detriment on the efficacy in TCL.

2. Histone Deacetylase (HDAC) inhibitors

a. Vorinostat (SAHA, Zolinza)

Vorinostat is a histone deacetylase inhibitor (HDACI). This group of drugs functions via modification of the epigenetic activities occuring within cells, which is to say the regulation of gene transcription by physical alterations of either DNA or the structural components of chromatin [66]. While a detailed discussion of the mechanism of HDACI's is beyond the scope of this paper, clinical success in epigenetic modulation has been largely seen via the histone deacetylase pathways [67].

Phase I data on vorinostat as an oral agent in treatment of a variety of hematologic malignancies (AML, CLL, MDS, ALL and CML) revealed a maximum tolerated dose and showed one CR, 2 CR's without recovery of platelets, 1 PR and 5 complete marrow responses [68]. A subsequent phase 2 trial looking at oral vorinostat exclusively in the setting of refractory CTCL demonstrated a PR in 8 of 33 patients with fairly good tolerance [69]. Pruritus relief was observed in almost 50% of patients, as well. Vorinostat recently gained FDA approval as a single agent drug for treatment of CTCL [70]. This decision was based on another phase IIb trial again exclusively looking at refractory CTCL [71]. In this landmark trial, 74 patients (including 61 patients with stage IIB or higher, 30 with SS and 22

with tumor disease) were enrolled with an overall response rate of 29.7% and a time to progression of 4.9 months overall. Toxicities were minimal in this study.

b. Depsipeptide (Romidepsin)

Along with vorinostat, other HDACI's have been examined, including depsipeptide (FK 228, Romidepsin). An early case report demonstrated partial response in 3 patients with CTCL and a complete response in 1 patient with PTCL [72]. This case report came from a subsequently published phase I trial that enrolled 37 patients, all with solid tumors of various types [73]. Subsequent evaluation of depsipeptide in HTLV-1-infected T-cell lines as well as in HTLV-1-engrafted mice showed inhibition in vitro as well as in vivo, with tumor shrinkage demonstrated in the mice [74]. Another study of a human T-cell lymphoma cell line showed that depsipeptide caused substantial apoptosis without significant cell cycle arrest as well as an additive toxicity when combined with denileukin difitox [75]. Combinations of depsipeptide with cytarabine, carboplatin, doxorubicin, etoposide, cyclophosphamide, 6-mercaptopurine and irinotecan in multiple cell lines showed additive effects, as well [76]. These studies in preclinical models help to show the general sensitivity of T-cell lymphomas to HDACi's.

Final results from a multi-institutional phase II trial of depsipeptide (given at 14 mg/m2 as a 4-hour infusion on days 1, 8 and 15 of a 28-day cycle) in patients with cutaneous T-cell lymphoma who had disease that had progressed or was refractory to multiple prior therapies were recently presented [ASH meeting 2008 abstract 1568]. Seventy-one patients were treated with overall disease control (CR+PR) of 62% in all patients and 70% in those receiving 2 cycles. Median duration of response (DOR) was 11 months (mo) and the maximum DOR as of data cut-off was 5.5+ years. The most frequent drug-related AEs were generally mild, including nausea, fatigue, hemoglobin decreased, and platelet count decreased. Refractory PTCL was treated by the same group on the same schedule with an ORR of 39% in all patients and 55% in patients who could receive 2 or more doses [ASH meeting 2008 abstract 1568].

c. LBH589 (panobinostat)

LBH589, a novel HDACI, underwent successful preclinical invesigations against human chronic myelogenous leukemic and acute leukemic cells as well as against myeloma cells [77,78]. A recent phase I study of this HDACI on 15 patients with primarily acute myeloid leukemia showed transient improvements in disease with a major dose-limiting toxicity of prolongation of the QT interval [79]. Recent phase II data presented at ASCO on panobinostat (20 mg) administered orally on days 1, 3, and 5 weekly until disease progression or intolerance showed PR for 3 patients, SD for 4 patients, and PD for 3 patients previously treated with bexarotene [ASCO meeting 2008 abstract 8555]. Most common (>15%) AEs (all grades) include diarrhea, thrombocytopenia, fatigue, asthenia, hypertriglyceridaemia, dysgeusia, nausea and pruritus.

d. PXD-101 (belinostat)

Similar to LBH589, PXD101, another novel HDACI, has not been well studied in T-cell disorders specifically but has shown significant synergism with bortezomib in multiple myeloma cell lines [80]. Various solid tumor cell lines have also shown susceptibility to this class of HDACI's, with further study in T-cell disorders being again warranted. A recent phase I study looking at a variety of hematologic malignancies (primarily of B-cell origin) showed activity as well as tolerability but offered little data in terms of T-cell malignancies [81].

3. Proteasome Inhibitors

a. Bortezomib

Bortezomib (Velcade, PS-341) is a selective, reversible inhibitor of the proteasome that has shown marked inhibitory activity in a variety of cell lines in both hematologic and solid malignancies [82]. Bortezomib has been most extensively studied clinically in the setting of multiple myeloma [83]. Encouraging data have been procured for using bortezomib in treating non-Hodgkin's lymphomas of a variety of types [84]. Pre-clinical data support the use of bortezomib in T-cell diseases [85]. A phase II trial of bortezomib as single agent therapy in CTCL and PTCL examined in its final analysis 12 patients (10 with CTCL, 2 with PTCL) with an overall response rate of 67% [86]. 2 CR's and 6 PR's were observed with relatively modest toxicities. These results support further investigation of bortezomib as a single agent or in combination in these diseases.

4. Conventional Cytotoxic Drugs and Anti-Metabolites

a. Pralatrexate

Pralatrexate is a folate analog with well-described anti-tumor effects that have been demonstrated as greater than methotrexate in murine models [87]. This antifolate enters malignant cells selectively as compared with methotrexate via reduced folate transporter (RFC-1), a fetal oncoprotein expressed exclusively on malignant and fetal tissue that efficiently transports reduced natural folates as a means to meet those cells' increased metabolic demands. The appeal of this drug is enhanced by its uptake into malignant cells at a nearly 14-fold rate compared to that of methotrexate, suggesting that the systemic toxicities of high-dose methotrexate could be avoided. A recent report examined the use of pralatrexate dosed at 135 mg/m2 every other week in 16 patients with B-cell lymphomas and 4 patients with T-cell lymphomas (PTCL NOS, T-cell ALL, HTLV-1 ATLL and panniculitic T-cell NHL) [89]. This phase I/II study demonstrated all 4 patients with various aggressive T-cell lymphomas achieving a complete response lasting from 3 to greater than 16 months.

Initial results of the PROPEL trial, a pivotal phase II, single-arm, nonrandomized, open-label, multi-center study and the largest prospective study in pts with PTCL, were recently presented [ASH meeting 2008 abstract 261]. On this study, patients received 30 mg/m2 of pralatrexate intravenously (IV) weekly for 6 of 7 weeks in addition to vitamin B12 and folic acid supplementation. Interim data were available for the first 65 evaluable patients (of 107 total patients), who had all failed a median of 3 prior regimens. The majority (35%) had PTCL NOS. Nineteen of 65 patients responded (29%). Of the 19 responders, 17 patients had evaluation by positron emission topography (PET) scan with 8 patients deemed to have a CR and 9 a PR. ORR as assessed by study investigators showed that 45% (n=29) of pts experienced either a CR or PR. The most frequently reported Grade (Gr) 3–4 AEs were thrombocytopenia (20 pts [31%]), mucositis (9 pts [14%]), anemia (8 pts [12%]), and neutropenia (7 pts [11%]).

b. Gemcitabine

Gemcitabine is a pyrimidine analog and well-studied chemotherapeutic agent. Multiple studies have demonstrated its use in PTCL and CTCL. A phase II trial of 13 patients (8 with PTCL, 5 with CTCL) demonstrated 1 complete response and 8 partial responses using gemcitabine 1200 mg/m2 given on days 1, 8 and 15 of a 28-day cycle [89]. Building on this data, a prospective phase II trial of the same dose of gemcitabine in mycosis fungoides (30 patients) and PTCL (14 patients) observed 5 CRs and 26 PRs [90]. 70.5% of patients had either a PR or CR. All of the patients had had pretreatment in these phase II trials. A phase II

trial of the same dose of gemcitabine as frontline therapy in CTCL looked at 32 patients with MF, PTCL or SS [91]. Of these patients, 7 achieved a CR and 17 achieved a PR (total response rate of 75%) with a very modest toxicity profile. Another phase II trial employing gemcitabine at 1000 mg/m2 on the same schedule as monotherapy in CTCL demonstrated a comparable ORR (68%) in 25 patients with CTCL [92].

c. Pegylated liposomal doxorubicin (Doxil)

Doxorubicin is an anthracycline used often in a variety of non-Hodgkin lymphomas. Pegylated liposomal doxorubicin (Doxil) given at a dose of 20 mg/m2 monthly was first studied in CTCL in a phase I/II trial with 10 patients, where the best response was CR in 6 patients and a PR in 2 patients with an ORR 80% [93]. A subsequent, multicenter phase I/II study looked Doxil at varying dose of 20-40 mg/m2 in 34 patients with CTCL where 15 patients achieved CR and 15 patients achieved PR for an ORR 88.2% [94]. Another recent phase II trial enrolled 19 patients with advanced/recalcitrant CTCL [95]. Similarly, investigators observed ORR 84.2% and CR 42.1%. In all these studies, adverse events were very mild and quickly resolved.

d. Pentostatin

Pentostatin is a purine analog and showed promise in early, smaller studies of CTCL [96]. Based on this, a phase I/II trial looked at 3.75-5.0 mg/m2 given intravenously for 3 days on a 21-day cycle in 24 patients with, on average, 3 prior therapies [97]. 17 patients had either a PR or CR, with an ORR 71%. A subsequent phase I/II trial with 42 patients demonstrated an ORR 54.8% [98]. The median duration of response was 4.3 months. Similar to other cytotoxic agents, a reasonable response rate and toxicity profile can be seen with this agent.

e. Forodesine (BCX-1777)

Forodesine (BCX-177; immucillin H) is a novel, small, transition-state inhibitor of purine nucleoside phosphorylase (PNP) [99]. The rationale for the clinical development of forodesine originated from the fact that children with mutations in the gene encoding for PNP have profound and selective T-cell lymphopenia [100]. As a transition state molecule, forodesine is not incorporated into DNA and, as a consequence of the PNP inhibition, forodesine alters the normal nucleoside pathway resulting in intracellular accumulation of 2’-deoxyguanosine triphosphate (dGTP) and, eventually, lymphocytes death [101].

Forodesine has shown significant in vitro activity with inhibition of proliferation of activated human T lymphocytes and acute lymmphoblastic leukemic T cells [102]. Based on these encouraging in vitro observations, Phase I and II clinical trials of forodesine were initiated in patients with refractory CTCL [103] as well as with other hematologic malignancies [104]. In a Phase I dose ranging study [ASH meeting 2004 abstract 2491], 13 CTCL (MF and SS) patients were treated with IV forodesine at doses of 40, 60, 90 or 135 mg/m2, every 12 hours over 5 days, with two week rest period before the next cycle. IV forodesine showed an excellent safety and tolerability profile and, as a secondary objective of the study, 3 patients achieved a CR, 1 PR and 6 SD. Based on the result of this Phase I trial and considering that IV formulation requires prolonged day infusion with increased risk of catheter infection, forodesine in oral formulation was evaluated in a Phase I/II multi-center dose escalation study for safety and efficacy in refractory CTCL patients [ASH meeting 2006 abstract 2467]. The 80 mg/m2 once daily was identified as the optimal biologic dose, and of the 36 patients treated with this dose, 2 achieved a CR, 12 a PR and 22 a SD. Forodesine was well tolerated with fatigue, nausea, peripheral edema and hedache, being the most frequent side effects. Importantly, no opportunistic infections and CMV reactivation were noted. Based on the preliminary results of this trial, a second Phase II multi-center trial with oral forodesine at a dose of 200 mg daily was initiated.

5. Immunomodulatory and Other non-Cytotoxic Drugs

a. Interferons

Interferons (IFN) are a family of secretory glycoproteins that are produced in response to a variety of viral and non viral inducers. IFN induce multiple biologic activities and have antiproliferative, antiviral, cytotoxic, and anti-angiogenic activity. IFN induce pro-apoptotic genes, reduce antiapoptotic genes, and modulate differentiation [105]. Recombinant alpha interferon has been used in the treatment of cutaneous T-cell lymphoma for almost two decades. A long-term follow of 51 patients with mycosis fungoides and Sézary syndrome treated with low dose alpha interferon as monotherapy was completed [106]. The patients ranged from stage Ia through stage IV with most stage IIb and stage III (Sézary syndrome). The mean follow-up period was 43.4 months. The results showed 21 complete remissions, 13 partial remissions, and 17 patients with stable or progressive disease. The mean time to complete remission was 4 months. Low-dose oral bexarotene in combination with low dose alpha interferon lead to rapid improvement in two patients with erythrodermic CTCL and one with follicular MF [107]. A study of 22 patients with stage IB through stage IV CTCL did not demonstrate any benefit with the addition of interferon alpha -2B to oral bexarotene over oral bexarotene alone [108]. A prospective controlled trial of stage II CTCL with interferon alpha-2a and extracorporeal phototherapy was conducted [109]. Patients with CTCL stage IIa with combination therapy achieved a response rate of 60% and patients with stage IIb only 25%. A multicentric prospective Phase II clinical study of 89 patients with early-stage IA to IIA MF treated for 14 months with low-dose IFN alpha 2b (6-18 mu/wk) and PUVA was completed [110]. A complete remission (CR) was obtained in 84% with an overall response rate of 98%. Sustained remissions were obtained in 20% of patients. High CD8+ counts were associated with a lower relapse rate. A phase II trial involving 63 patients with all stages of MF was conducted and 55 patients were treated with escalating doses of IFN alpha-2a combined with PUVA for one year [111]. PUVA was then continued as maintenance indefinitely. A complete response (CR) was obtained in 74.6% and partial response (PR) in 6%. The median response duration was 32 months, 5 year survival was 91%, and 5 year disease-free survival was 75%. Adjuvant alpha-interferon does not appear to benefit total skin electron beam irradiation. In one study, interferon did not appear to increase CR rate, disease-free survival, or overall survival [112]. Recently, peginterferon alfa-2b has been reported to be efficacious for MF [113]. A patient with CTCL and chronic HCV infection received peginterferm alph-2b plus ribavirin. Peginterferon alpha-2b was injected 80 micrograms subcutaneously once a week. The patient's cutaneous lesions showed dramatic improvement in four weeks. The side-effects of interferon therapy are dose dependent. They include fatigue, neutropenia, leukopenia, fever, myalgia, nausea, vomiting, and headache. Liver and thyroid functions may be altered [105].

b. Toll Receptor Agonists

Toll-like receptors (TLR5) 2, 4, and 9 expression patterns have been studied in mycosis fungoides, Sézary syndrome, atopic dermatitis, and psoriasis [114]. TLR2, TLR4, and TLR9 expression was low in atopic dermatitis and psoriasis, but very strong in the epidermis with mycosis fungoides. TLR expression in Sézary syndrome was intermediate between atopic dermatitis and mycosis fungoides. Imiquimod is an immunomodulatory agent, which is FDA approved for the treatment of external genital warts, actinic keratosis, and superficial basal cell cancers. It is an activator of TLR7. In vivo, it is a potent inducer of tumor necrosis factor alpha, interferon gamma, and interferon alpha [115]. Imiquimod 5% cream was evaluated in the treatment of six patients with stage IA to IIB mycosis fungoides [116]. The cream was applied three times per week for twelve weeks and index lesions were biopsied pre and post treatment. Histologic clearance of index lesions was demonstrated in three of six patients. Significant improvements in clinical scores were noted for all treated lesions.

Topical application of imiquimod was previously reported to be helpful in the treatment of stage IA cutaneous T cell lymphoma [117]. A patient with CD30+ anaplastic large cell lymphoma and two of four patients with mycosis fungoides were reported to have a complete clinical remission with topical imiquimod [118]. Imiquimod may be helpful in treating sanctuary lesions or resistant lesions in patients undergoing PUVA for CTCL [119] CPG 7909 is a TLR9 modulator that was investigated in 28 patients with 7 (25%) achieving objective clinical response (5 with PR and 2 with CR) [ASH meeting 2004 abstract 743]. Eleven patients maintained stable disease SD, while 10 had PD. Recent data have shown that clinical responses with adenovirus-mediated gene transfer in CTCL are associated with induction of type-1 an type-2 IFN gene signatures, including TLR [120].

c. Denileukin diftitox

Denileukin diftitox has been approved by the FDA for the treatment of refractory cutaneous T-cell lymphoma with CD25+ expression. The drug represents a fusion protein containing interleukin-2 (IL-2) and the diphtheria toxin A chain, which binds to the IL-2 receptor on the T-cell lymphoma cells. After binding the receptor, the drug is internalized into the cell and the receptor and the diphtheria toxin are cleaved from the fusion protein. Cleavage in the endosome releases the diphtheria toxin into the cytosol, which inhibits cellular protein synthesis and results in rapid cell death [121]. The high-affinity human IL-2 receptor is composed of three membrane proteins: the 55 kD IL-2Rα chain (TAC, CD25), the 70-75 kD IL-2Rβ chain (CD122), and the 64 kD IL-2Rγ chain (CD132). Ex vivo studies demonstrate the denileukin diftitox best interacts with the high (CD25/CD122/CD132) affinity IL-2 receptors on the cell surface and undergoes internalization [121]. In one study of 24 patients, clinical response to denileukin diftitox was observed in 78.5% of patients with high CD25 expression versus 20% with low or undetectable CD25 expression [122]. A pivotal phase III trial of two dose levels of denileukin diftitox was conducted for the treatment of cutaneous T-cell lymphoma [123]. The patients entered in the study had stage Ib to IVa disease with biopsy proven CTCL that expressed CD25 on ≥ 20% of lymphocytes. Patients were assigned to one of two dose levels (9 or 18 mcg/kg/d) of denileukin diftitox, the drug was administered for five consecutive days every three weeks for up to eight cycles. Of the 71 patients, 20% had a partial response and 10% had a complete response. The median response rate was 6.9 months (range 2.7 to 46.1 months). There was no statistical difference between the two doses.

In a single-center series of 37 patients with early and advanced CTCL, the response and survival following denileukin diftitox administration was evaluated at doses of 9 mcg/kg and 18 mcg/kg per day [124]. In eight patient with early stage disease (< IIA), the overall response was 62.5% with 70% of patients still alive at 46 months. In 29 patients with advanced-stage (≥ IIB), the overall response was 49.3% and the median survival was 31 months. A decrease in lactate dehydrogenase was strongly correlated with a clinical response. A study on quality-of-life (QOL) improvements in CTCL patients treated with denileukin diftitox demonstrated that patients with advanced and /or recurrent CTCL who responded showed significant improvements in self-rated overall QOL, skin appearance and pruritus severity [125].

Most recently, an integrated analysis of 3 large phase III, placebo-controlled trials of denileukin difitox in CTCL was presented [ASCO meeting 2008 abstract 8551]. Denileukin difitox doses were 9 or 18 μg/kg IV given daily for 5 days with cycles repeating every 21 days and a maximum of 8 courses. A small number of CD25-negative patients were included. The ORR in those treated with denileukin difitox (263 patients total) was 38.0% versus 15.9% in those treated with placebo (44 patients total). Most impressive was a median PFS of 794 days for those who received the drug versus 124 days in those who received placebo.

Adverse side-effects secondary to denileukin diftitox were reported in the pivotal phase III trial [123]. Flu-like symptoms were common, including fever, chills, nausea, vomiting myalgias, and arthralgias. Acute infusion-related events were noted, including hypotension, dyspnea, chest pain, and back pain. A vascular leak syndrome of clinical significane was reported, manifesting as hypotension, hypoalbuminemia, and edema. Transient elevations in hepatitic transaminases were noted in 61% and hypoalbuminemia in 79%.

6. Signal Transduction Inhibitors

a. Enzastaurin

Enzastaurin is an oral small molecule serine/threonine kinase inhibitor that has been shown to target PKC β and PI3K/AKT pathways [126]. These pathways play a role in inhibition of apoptosis in lymphoma and carcinoma cell lines and are are also important in tumor-induced angiogenesis [127]. The membrane-bound enzyme phospholipase C and IP3 aid in transmitting surface receptor signals into the cell by phosphorylation of PKC β and PI3K/AKT. This induces a series of downstream cell signals that result in inactivation of pro-apoptotic molecules like caspase-9, Bad, forkhead family of transcription factors, GSK3 β and RP S6 and paves the road for unrestrained proliferation of malignant cells [128, 129]. Investigators have recently shown that enzastaurin blocks the phosphorylation of PKC β and AKT in the CTCL lines HH and HuT-78. This resulted in a dose-dependent inhibition of cell proliferation and induction of apoptosis in-vitro [130]. Similar results have been previously reported in cell lines and xenografts of B cell lymphoma, multiple myeloma and Waldenstrom's macroglobulinemia [127, 131,132]. Clinical experience with enzastaurin in lymphoma is still very limited. In a phase II study 55 patients with relapsed or refractory diffuse large B cell lymphoma were treated with 525 mg oral enzastaurin daily for continuous treatment cycles of 28 days. Twenty-four patients were free from disease progression for more than two treatment cycles. In general, treatment was well tolerated and most common side effects effects were diarrhea, fatigue and nausea [132]. A phase II study in CTCL is in progress.

Future Developments

Novel drug classes and targets continue to come to the forefront in the treatment of TCL. Recently, the BIRC5 gene was shown to be upregulated in TCL, presenting a novel target in this disease [133]. The B-cell receptor complex-associated tyrosine kinase SYK has come to light as an important therapeutic target in B-cell NHL [134], and fostamatinib disodium, a highly specific SYK inhibitor, recently has shown promising activity in a Phase II clinical trial [ASH meeting 2008 abstract 3]. Interestingly, SYK is also strongly expressed in PTCL (but not in normal T-cells), suggesting that SYK inhibition might be active in PTCL without significant T-cell immunosuppression [135]. Another very interesting agent is the oral mTOR inhibitor everolimus, which in a small phase II study showed encouraging activity in both CTCL and PTCL (Johnston PB et al. 2008 Lugano International Lymphoma Meeting, Abstr. #262a).

In terms of ongoing discovery in immunologic therapies, delivery of adenovirus-mediated intralesional interferon-gamma gene transfer has been shown to induce tumor regression in cutaneous lymphomas [136]. More recent data has demonstrated in vivo induction of vector-dependent and transgene-dependent gene signature in skin lymphoma lesions after adenoviral IFN-γ gene transfer, providing evidence supporting the beneficial role of vector-induced innate response in tumor regression. [120] The oral mTOR inhibitor everolimus has recently been dosed at 10 mg orally once a day in 8 patients with refractory TCL. This drug was well-tolerated and showed and ORR of 63% [Lugano International Lymphoma Meeting

2008: abstract 262]. Targets like these will continue to be important points of exploration for future treatments.

The cornerstone of treating PTCL and refractory CTCL, however, continues to be CHOP-based chemotherapy [137]. Aside from ALK-1 positive ALCL, the prognosis in these entities continues to be quite poor relative to other NHL. The combination of CHOP-based regimens with novel therapeutics will likely prove to be the mainstay of future trials. Alternative chemotherapy regimens have been utilized in trials recently, including non-anthracycline-based combinations, and these have proven to be as good as CHOP from the perspective of OS and EFS [ASH 2006 meeting abstract 2464].

Conclusions

Effectively treating the wide spectrum of TCL remains a difficult and multifaceted horizon of lymphoma management. Outside of early-stage Mycosis Fungoides, pcALCL, and ALK-1-positive ALCL, the prognosis in these malignancies remains quite poor. To determine the most rational and focused application for the multitude of therapeutic agents and combinations currently available for these diseases is now the biggest challenge.

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Table 1

Salient Clinicopathological and Biological Features of The Major Types of Mature T/NK Cell Lymphomas.

Entity	Pathological Features	Clinical Features
T-cell Prolymphocytic Leukemia (t-PLL)	Small to medium size lymphocytes, non-granular basophilic cytoplasm, usually CD4-negative, Inv(14)(q11;q32) with TCL-1 gene, trisomy 8, del(11)(q22.3-23.1) with ATM gene	Hepatosplenomegaly, generalized lymphadenopathy, anemia, thrombocytopenia. Progressive clinical course.
T-cell Large Granular Lymphocyte (LGL) Leukemia	Circulating LGL, may have atypia or immaturity; usually CD8-positive with variable expression of CD57 and CD16.	Lymphocytosis and neutropenia, often asymptomatic, rheumatoid arthritis, autoantibodies; bone marrow involved, usually indolent, non-progressive
NK-cell Leukemia	Circulating LGL, with atypia and immaturity, typically sCD3-negative, CD56-positive, TIA/Granzyme/Perforin-positive, often EBV-positive.	More prevalent among Asians and younger adults; fever, hepatosplenomegaly, variable lymphoadenopathy, circulating atypical lymphocytes, highly aggressive, multiorgan failure.
Adult T-cell Leukemia/Lymphoma (ATLL)	Histology variable; usually CD7-negative, CD4/CD25 positive, clonally integrated HTLV-I.	Endemic in Japan, Caribbean, Brazil; four clinical types: acute leukemic, lymphomatous, chronic and smoldering. Frequent cutaneous lesions, hypercalcemia, lytic bone lesions; rapid progressive course.
Angioimmunoblastic T-cell Lymphoma (AITL)	Polymorphic T-cells, often clear cells, arborizing vessels, eosinophils and plasma cells, increased FDC outside of the GC; usually CD4-positive but often CD8-positive cells present, typically CD10-positive; many EBV-positive B-cells, often oligoclonal or monoclonal; trisomy 3, 8, X with frequent unrelated clones.	Lymphadenopathy, hepatosplenomegaly, advanced stage, B-symptoms, skin rash, hypergammaglobulinemia, Coombs-positive hemolytic anemia; prognosis poor. Risk of developing B-cell lymphomas.
Peripheral T-cell Lymphoma NOS (PTCL)	Histology variable. Usually CD4-positive; extranodal forms often TIA/Granzyme/Perforin-positive, complex chromosomal aberrations.	Wastebasket category; clinical course variable but generally aggressive; advanced stage; lymphadenopathy, cure rate low (25%).
Anaplastic Large Cell Lymphoma, CD30-positive, T/Null-cell, Systemic (CD30+ ALCL)	Large cells with eccentric nuclei and Golgi-like inclusions, wreath-like nuclei, abundant cytoplasm, not all tumor cells are very large or pleomorphic, some are small and monomorphic (variants); common sinusoidal infiltration; CD30-positive, EMA-positive, often CD45-negative, CD15-negative, T-cell markers variable, often TIA/Granzyme/Perforin-positive; t(2;5)-positive subset with overexpression of ALK (ALK-1) has best prognosis.	Used to be called Ki1-lymphoma; Ki1 antigen now known as CD30; lymphadenopathy, extranodal sites (skin), bimodal age distribution, advanced disease, B-symptoms, aggressive course; responds well to therapy and cure rate high (75-80%) for the ALK-1-positive subset (younger patients).
Mycosis Fungoides (MF)	Epidermotropic CD4-positive, CLA-positive, CD7-negative, CD26-negative cells, cerebriform nucleus	Adults, multiple skin lesions in patch, plaque and tumor stage; indolent but progressive.
Sezary Syndrome (SS)	Circulating small lymphoid cells with cerebriform nucleus, ocasionally large cells; CD4-positive, CD7-negative, CD26-negative.	Adults, erythroderma, often generalized lymphadenopathy, blood and bone marrow involvement; unfavorable prognosis (about 3 years MS).
Primary Cutaneous CD30-positive T/Null-cell lymphomas	Large CD30-positive lymphoid cells, variable T-cell markers, usually anaplastic features but may be typical large cell; cytology has no prognostic significance; lack t(2;5) and is ALK-1-negative.	Adults, usually solitary lesions, nodular, may be ulcerated; no systemic disease on staging, highly favorable prognosis, progression to systemic disease rare; need to distinguish from LyP.
Subcutaneous, Panniculitis-like T-cell Lymphoma	Subcutaneous lace-like lymphoid infiltrate with predominant small cells, rimming around fat cells common; usually CD8-positive, TIA/Granzyme/Perforin-positive; most cases are derived from αβ cells, some TCR; EBV negative	Subcutaneous nodules especially in the extremities, systemic/nodal dissemination rare, clinically variable, may have chronic course but can be aggressive, particularly when hemophagocytic syndrome develops.
NK/T-cell Lymphoma, Nasal and Nasal-type	Variable cytology, angioinvasive and angiodestructive (originally called angiocentric lymphomas), common necrosis and apoptosis; typically CD2-positive, TIA/Granzyme/Perforin-positive, sCD3-negative, CD5-negative, CD56-positive; almost always EBV-positive; TCR not rearranged.	More common in Asia, Central (Mexico), and South America; mostly adults, nodal involvement rare. Nasal form presents with destructive lesion in the nose, sinuses, upper palate; usually early stage but aggressive and prognosis poor. Nasal-type involves the skin, soft tissues, GI tract, and testis.

Entity	Pathological Features	Clinical Features
T-cell Lymphoma, α/β *vs* γ/δ - type, hepatosplenic and non-hepatosplenic	Monotonous, medium-size cells infiltration in liver, spleen red-pulp, marrow, sinusoidal pattern; typically CD3-positive, CD56 variable, TIA-positive, Granzyme/Perforin variable; mostly TCRδ1+, occasionally α/β type.	Young adults, male predominance, marked hepatosplenomegaly, no lymphoadenopathy, bone marrow usually involved, occasional leukemic involvement; aggressive course; relapse the rule, non curable.
Enteropathy-associated T-cell lymphoma (EATL)	Broad cytological spectrum, epitheliotropism common, ulceration common, adjacent mucosa shows features of enteropathy, with villous atrophy, increased intraepithelial small lymphocytes, CD103-positive (integrin); typically TIA/ Granzyme/Perforin-positive	Most patients have adult-onset celiac disease (CD) or are diagnosed with CD at the time of EATL presentation; abdominal pain, diarrhea, often small bowel perforation; prognosis poor.